



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/20, 31/07, 31/355, 31/44, 31/455, 33/04, 33/30 // (A61K 33/30, 31:07, 31:355, 31:44, 31:455, 33:04)	A1	(11) International Publication Number: WO 98/48788 (43) International Publication Date: 5 November 1998 (05.11.98)
(21) International Application Number: PCT/GB98/01260 (22) International Filing Date: 23 April 1998 (23.04.98) (30) Priority Data: 9708700.1 29 April 1997 (29.04.97) GB 9708703.5 29 April 1997 (29.04.97) GB (71) Applicant (for all designated States except US): SCOTIA HOLDINGS PLC [GB/GB]; Weyvern House, Weyvern Park, Portsmouth Road, Peasmarsh, Guildford, Surrey GU3 1NA (GB). (72) Inventor; and (75) Inventor/Applicant (for US only): HORROBIN, David, Frederick [GB/GB]; Kings Park House, Laurelhill Business Park, Stirling FK7 9JQ (GB). (74) Agent: FARWELL, William, Robert; Phillips & Leigh, 7 Staple Inn, Holborn, London WC1V 7QF (GB).	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: TREATMENT OF DEPRESSION AND ANXIETY USING DOCOSAHEXAENOIC ACID OR NATURAL ANTIOXIDANTS		
(57) Abstract Medicament manufacture for depression or anxiety using compositions of natural antioxidants, or compositions of essential fatty acids (docosahexaenoic acid, DHA) optionally with essential nutrients and/or natural antioxidants.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

TREATMENT OF DEPRESSION AND ANXIETY USING DOCOSAHEXAENOIC ACID OR NATURAL ANTIOXIDANTS

The invention relates to treatment of depression and anxiety.

GENERAL

Depression and anxiety are among the commonest health problems. Although one can occur without the other, it is also common for the two to occur together since in some respects they appear to be closely related. Around 30% of the population experience an episode of depression or anxiety at some time in their lives. This may often be passed off by using expressions such as "feeling down" or "feeling blue" or being unduly worried. As well as being the cause of great unhappiness for both individuals and those who come into contact with them, depression is dangerous as it is by far the commonest cause of suicide.

The n-3 essential fatty acids (EFAs) are important structural elements of the brain. They are required for normal function of all nerve cells. The n-6 EFAs are also important components of nerve cell membranes. The two types of EFA are metabolised by the pathways shown in Table 1.

TABLE 1

<u>n-6 EFA's</u>		<u>n-3 EFA's</u>
18:2n - 6		18:3n - 3
(Linoleic acid, LA)		(α -Linolenic acid, ALA)
↓	delta - 6 desaturase	↓
18:3n - 6		18:4n - 3
(γ - Linolenic acid GLA)		(Stearidonic acid)
↓	elongation	↓
20:3n - 6		20:4n - 3
(Dihomo - γ - linolenic acid, DGLA)		
↓	delta - 5 desaturase	↓
20:4 n-6		20:5 n-3
(Arachidonic acid, AA)		(Eicosapentaenoic acid, EPA)
↓	elongation	↓
22:4n - 6		22:5n - 3
(Adrenic acid, AdrA)		
↓	delta - 4 - desaturase	↓
22:5n - 6		22:6n - 3
		(Docosahexaenoic acid, DHA)

The acids, which in nature are of the all - cis configuration, are systematically named as derivatives of the corresponding octadecanoic, eicosanoic or docosanoic acids, e.g. LA *z,z*-octadeca - 9,12 - dienoic acid or DHA *z,z,z,z,z,z* - docosa-4,7,10,13,16,19 - hexaenoic acid, but numerical designations based on the number of carbon atoms, the number of centres of unsaturation and the number of carbon atoms from the end of the chain to where the unsaturation begins, such as, correspondingly, 18:2 n-6 or 22:6 n-3, are convenient. Initials, e.g. EPA, and shortened forms of the name e.g. eicosapentaenoic acid, are used as trivial names in some instances.

PRESENT WORK

In one aspect of the present work the applicants have noted that three groups of investigators have suggested that in depression there may be a reduced ratio of n-3 EFAs to n-6 EFAs (J.R. Hibbeln et al Am J. Clin. Nutr. 1995 62 1-9; M. Maes et al J. Affective Dis. 1996 38 35-46; P.B. Adams et al Lipids 1996 31 5-157-61) but no actual deficiency of n-3 EFAs has been demonstrated.

However, the applicants have recently measured EFA concentrations in the red blood cell phospholipids of patients with depression and compared these levels with those in normal, control individuals. In normal individuals (n=15) the concentration was 5.43 ± 2.01 mg/100mg lipid whereas in matched depressed individuals (n=15) the concentration was 3.11 ± 2.47 mg/100mg lipid. This difference was very highly significantly statistically at $p > 0.009$. This demonstrates that in depression there is a deficiency of DHA in red blood cell membranes. The other investigators quoted above did not measure DHA levels in cell membranes and did not demonstrate any actual deficiency of DHA in depression. Since red blood cells are a guide to what happens in the brain, this demonstrates that brain DHA levels are probably reduced.

A deficiency of a substances does not necessarily mean that the substance can be used in therapy. The have applicants therefore tested the administration of DHA in three patients who had developed moderate to severe depression. The aim was to find out whether DHA could relieve depression and, if so what dose might be effective.

The patients were treated with capsules of DHA in triglyceride form and each dose was given for a period of eight weeks. At a dose of 250mg DHA/day, the patients experienced no improvement in depression score. At 500mg/day, two patients experienced a moderate but not complete improvement, but the third experienced no change. At 1g/day the third patient experienced a modest improvement and in the two patients who had improved on 500mg./day there was near complete resolution of symptoms. At 2g/day the two patients who had recovered

remained completely recovered. The third patient improved further but without complete resolution.

These observations show that DHA is able to treat depression and that the effective dose is 350 to 3000mg/day, though higher doses up to for example 10g day could be given.

In another aspect of the present work the applicants have noted that there are many drugs which are able to treat depression and anxiety. However, these do not work in between 25 and 50% of patients. Even when they do work, in some patients they cause side effects such as dry mouth, gastro-intestinal disturbances, excessive sleepiness, blood pressure disturbances, impotence in males, inability to experience orgasm in both sexes, and vague unpleasant feelings or dysphoria which can be very distressing to the patient. There is therefore a considerable need for new approaches to depression.

There is recent evidence that depression and anxiety may be associated with reduced levels of the highly unsaturated n-3 essential fatty acids (Maes M. et al, J. Affective Disorders 1996 38 35-46; Hibbeln J. et al, Am. J. Clin. Nutr. 1995 62 1-9 as cited earlier herein). There may be many reasons for this including inadequate intake of the n-3 EFAs, or abnormalities in desaturation and elongation. Another possibility, however, is that the reduced levels of n-3 EFAs in blood are caused by increased exposure to oxidants such as cigarette smoke or car exhaust fumes or by inadequate intakes of the many different nutritional factors which contribute to the total antioxidant activity of the body, given that n-3 EFAs are highly susceptible to oxidation.

The antioxidant systems of the body are very complex and require the close interaction of many different compounds. Just as providing large amounts of one B vitamin could not compensate for the deficiencies of other B vitamins, so supplying one component of the antioxidant system cannot compensate for others which may be missing. Most clinical trials of antioxidants have made the mistake of giving large amounts of one or other antioxidant without attempting to provide a balanced intake

of all the likely antioxidants and related co-factors. The applicants have therefore carried out a study in which those antioxidants and related co-factors most likely to be deficient in normal people were provided and compared with placebo for their effects on depression. The materials which were provided were ascorbic acid (100mg), pyridoxine hydrochloride (25mg), beta-carotene (3mg), vitamin E (100mg), zinc (4mg), nicotinamide (10mg) and selenium (450 microg). The figures in brackets represent the amounts provided each day. Placebo capsules contained coconut oil.

The study was performed in patients with peripheral vascular disease who have a known tendency to have depressed mood. 120 patients were entered into the study and by the randomisation process 55 were assigned to receive antioxidant and 65 to receive placebo. They were assessed at baseline on the Hospital Anxiety and Depression (HAD) Scale, a standard instrument for measuring these parameters. They were treated with the antioxidant or placebo for two years. The numbers of patients classified as anxious or depressed on the HAD anxiety and expression sub-scales are shown in Table 2:

TABLE 2

Percentages of patients in the study with anxiety or depression as defined by the Hospital Anxiety and Depression Scale.

	<u>Baseline</u>	<u>End of Trial</u>	<u>Change</u>
<u>Anxiety</u>			
Antioxidant group	27.6%	17.2%	-10.4%
Placebo group	30.8%	38.5%	+ 7.7%
<u>Depression</u>			
Antioxidant group	13.8%	6.9%	- 6.9%
Placebo group	5.1%	7.7%	+ 2.6%

Clearly during the treatment period the numbers of patients who were anxious or depressed decreased substantially in the antioxidant group but increased in the

placebo group. The differences between the changes in the two groups were significant at $p < 0.05$.

This study demonstrates that the combined antioxidant mix proposed is effective in improving anxiety and depression.

THE INVENTION

In one aspect the invention lies in use of DHA in a method of making a medicament for treating depression, anxiety, "feeling down" or "feeling blue", by the administration of DHA at 350 to 3g or more (up to 10g) per day, preferably 500 mg to 2g per day, and in such treatment itself. Other fatty acids of the n-3 series, such as alpha-linolenic acid (ALA), stearidonic acid (SA), eicosapentaenoic acid (EPA) and docosapentaenoic acid (DPA n-3) may optionally be added, as may fatty acids of the n-6 series such as linoleic acid (LA), gamma-linolenic acid (GLA), dihomogamma linolenic acid (DGLA) and arachidonic acid (AA), at 250 mg to 2000mg/day. Since patients with depression frequently fail to eat properly, the DHA may also optionally be provided with supplements of essential minerals and vitamins. In addition, because EFAs like DHA are easily oxidised, there are advantages in combining it with physiologically effective lipophilic antioxidant compounds such as vitamin E, alpha-lipoic acid and beta-carotene.

The DHA may be administered in any form which is able to raise the levels of DHA in the blood. The oral route is likely to be the one preferred, but topical or parenteral routes are also possible. Appropriate forms of DHA are triglycerides, diglycerides, mono-glycerides, free fatty acid, ethyl or other appropriate esters including derivatives of 1, 2- or 1, 3-propane diol or of geminal one-carbon diols, anhydrides, amides, cholesterol esters, phospholipids of any type or any other appropriate derivatives. Specific propane diol, geminal one-carbon diol and other derivatives are as disclosed in the applicant's specifications WO 96/34855 (PCT GB 96/01052) and WO 96/34846 (PCT GB 96/01053) to which attention is directed.

Use may be made of any appropriate delivery vehicle known to those skilled in the art such as capsules, emulsions, granules, powder, tablets or other appropriate form.

In another aspect the invention lies in the antioxidant mix discussed earlier, both as such and when used in preparation of a medicament for the treatment of anxiety, depression, "feeling down" or "feeling blue". Depression may be in terms of "the blues", unhappiness or feeling low, or any other manifestation of depressed mood, and the invention extends to the treatment itself.

The actives are as set out below in Table 3. The figures represent the daily dose to be administered. The daily dose may be provided in a single capsule, tablet or other solid or liquid dosage form known to those skilled in the art, or may be provided in divided doses to make up the full daily dose. The ingredients may be provided in any form assimilable after oral administration.

TABLE 3

<u>Active</u>	<u>Lower Limit</u>	<u>Upper Limit</u>
Vitamin C (ascorbic acid)	50mg/day	10g/day
Beta-carotene	2mg/day	100mg/day
Vitamin B6 (pyridoxine or other forms)	15mg/day	100mg/day
Zinc (as sulphate, gluconate or other forms)	2mg/day	50mg/day
Nicotinamide or niacin	5mg/day	100mg/day
Vitamin E	50mg/day	1000mg/day
Selenium (as selenite, selenate, conjugates such as selenomethionine, or other forms)	100microg/day	1000 microg/day

Each of the above compounds may be presented in any appropriate biologically available form.

The above are necessary actives in the formulation. To them may be added optionally other nutrients but in particular n-3 essential fatty acids such as alpha-linolenic acid (ALA), stearidonic acid (SA), eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA n-3) and docosahexaenoic acid (DHA). Such fatty acids may be provided in any appropriate form as discussed earlier herein, in a dose ranging from 10mg to 10g per day. Folic acid may also be a valuable nutrient in anxiety and depression and so it too may be added to the formulation in dose ranging from 10 to 1000 microg/day.

Examples

Formulations of DHA and their use against depression are illustrated below in Examples 1 - 12.

1. 250 mg soft gelatin capsules containing DHA in triglyceride, ethyl ester, diglyceride, monoglyceride, 1,3-propane diol ester, amide, phospholipid or other bioavailable form to be taken in a dose of 2 to 8 capsules per day.
2. 500 mg DHA capsules as in 1 to be taken at a dose of 1 - 4 capsules/day.
3. As 1 or 2 but with a multi-nutrient formulation either co-administered or forming part of the DHA capsules, with the recommended daily allowances of vitamins of the B group, vitamin C, vitamins A and D, folic acid, bioavailable zinc, selenium and magnesium, and optionally others of the known vitamins and essential minerals.
4. As 1, 2 or 3 but further with effective amounts of lipophilic antioxidants such as vitamin E, beta-carotene or alpha-lipoic acid.
5. 1000mg DHA capsules as in 1 to be taken at a dose of 1 - 2 capsules/day.

6. An emulsion containing DHA in a concentration of 350mg to 2g in 1 -10 ml to be taken in doses which provide 350mg to 2g/day. Any appropriate emulsifying agent may be used, but the galactolipids are particularly appropriate emulsifying agents. Reference may be made for them to the applicants' PCT specification SE 95/00115 (WO 95 20943) to which attention is directed.
- 7-12. As in examples 1 - 6 except that 250mg to 2g/day of each of one or more of ALA, SA, DPA, EPA, LA, GLA, DGLA or AA is also provided in the formulation.

Examples of antioxidant formulations as such or for use against depression or anxiety are:-

13. Capsules of ascorbic acid 100 mg, pyridoxine hydrochloride 25 mg, vitamin E 100 mg, available zinc 4 mg, nicotinamide 10 mg, beta carotene 3 mg and available selenium 450 microg, or one half or one quarter of those amounts, for administration to give those amounts daily.
14. Capsules as last with 100 mg eicosapentaenoic acid in addition.
15. Capsules as 13 or 14 with 100 microg folic acid in addition.
16. Capsules as 13, 14 or 15 with 200 mg docosahexaenoic acid in addition.

CLAIMS

1. A method of making a medicament for treatment of depression, anxiety, "feeling down" or "feeling blue", and such treatment itself, using DHA in bio-available form formulated for administration of 350mg to 3g DHA or more (up to 10g) per day, preferably 500mg to 2g.
2. As 1, but with 250 mg to 2g/day of each of one or more other fatty acids also, selected from ALA, SA, EPA, DPA, LA, GLA, DGLA or AA.
3. As 1 or 2, but also with effective amount(s) related to the recommended daily allowances of one or more other essential nutrients such as vitamins of the B group, vitamin C, vitamins A and D, folic acid, and bioavailable zinc, selenium or magnesium.
4. As 1, 2 or 3 but also with effective amounts of one or more lipophilic antioxidants such as vitamin E, alpha-lipoic acid or beta-carotene.
5. The formulation as in claim 1, 2, 3 or 4, per se.
6. A method of making a pharmaceutical or nutritional formulation for treatment of depression, anxiety, "feeling down" or "feeling blue", and such treatment itself, using ascorbic acid (50mg - 10g), beta-carotene (2mg - 100mg), Vit. B₆ (pyridoxine 15mg - 100mg or equivalent amounts of other forms), zinc (2mg - 50mg), nicotinamide or niacin (5mg - 100mg), vitamin E (50mg - 1000mg), and selenium (100 microg - 1000 microg) presented for administration in daily amounts in single or divided doses, each in biologically active form.
7. Method as in claim 6, which provides in addition for administration at 10mg to 10g per day of one or more of ALA, SA, EPA, DPA n-3 or DHA.

8. Method as in claim 6 or 7, which provides in addition for administration at 10 microg to 1000 microg/day of folic acid.
9. The formulations as in claim 6, 7 or 8, per se.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 98/01260

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/20 A61K31/07 A61K31/355 A61K31/44 A61K31/455
A61K33/04 A61K33/30 //(A61K33/30,31:07,31:355,31:44,31:455,
33:04)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 347 056 A (EFAMOL HOLDINGS) 20 December 1989 see page 5, line 1 - line 35; claims 1-3	1-5
Y	---	6-9
X	WO 96 34846 A (REDDEN PETER ;SCOTIA HOLDINGS PLC (GB); MANKU MEHAR (GB); PITT AND) 7 November 1996 cited in the application see page 29, line 8 - line 28 see page 28, line 11 - line 18	1-5
X	WO 96 34855 A (SCOTIA HOLDINGS PLC ;MANKU MEHAR (GB); PITT ANDREA (GB); KNOWLES P) 7 November 1996 cited in the application see page 22, line 8 - line 15 see page 23	1-5

	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

2 October 1998

Date of mailing of the international search report

15. 10. 98

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Seegert, K

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 98/01260

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	EP 0 440 341 A (EFAMOL HOLDINGS) 7 August 1991 see page 7, line 25 - line 43	1-5
Y	---	6-9
P,X	FR 2 749 133 A (MOREAU PIERRE) 5 December 1997 see page 13, line 16 - line 40	1-5
X	---	1-5
	HIBBELN J.R. ET AL: "Dietary polyunsaturated fatty acids and depression: when cholesterol does not satisfy" AM. J. CLIN. NUTR. (UNITED STATES), vol. 62, no. 1, 1995, pages 1-9, XP002071081 cited in the application see abstract	1-5
P,X	---	1-5
	IRMISCH G. ET AL: "Changes of the concentration of certain biochemical parameters in depressive patients depending on the severity of illness" PHARMACOPSYCHIATRY, vol. 30, no. 5, September 1997, page 184 XP002071082 see the whole document	1-5
P,X	---	1-5
	PEET M. ET AL: "Depletion of omega-3 fatty acid levels in red blood cell membranes of depressive patients" BIOL. PSYCHIATRY, vol. 43, no. 5, 1 March 1998, pages 315-319, XP002071083 see abstract	1-5
P,X	---	1-5
	PEET M. ET AL: "Lipids, depression and physical diseases" CURRENT OPINION IN PSYCHIATRY(UNITED KINGDOM), vol. 10, no. 6, November 1997, pages 477-480, XP002071084 see abstract	1-5
Y	---	6-9
	KOUDELOVÁ J. ET AL: "The natural antioxidant capacity in patients with major depression" HOMEOSTASIS IN HEALTH AND DISEASE (CZECH REPUBLIC), vol. 38, no. 1, January 1997, pages 2-3, XP002079305 see page 3	6-9

	-/--	

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 98/01260

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category ²	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>PETRIE W.M. ET AL: "Vitamins in psychiatry. Do they have a role?" DRUGS (AUSTRALIA). vol. 30, no. 1, 1985, pages 58-65, XP002079306 see page 59, left-hand column, last paragraph see page 62, left-hand column, last paragraph - page 63, left-hand column ---</p>	6-9
Y	<p>DOWNING D. ET AL: "Effective nutritional medicine: the application of nutrition to major health problems" J. OF NUTRITIONAL AND ENVIRONMENTAL MEDICINE (UNITED KINGDOM), vol. 6, no. 2, 1996, pages 191-232, XP002079307 see page 215, last paragraph - page 217 -----</p>	6-9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 98/01260

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-5

Method of making a medicament for the treatment of depression and anxiety using DHA and formulations thereof (Claims 1 - 5)

2. Claims: 6-9

Method of making a pharmaceutical or nutritional formulation for the treatment of depression and anxiety using specific amounts of ascorbic acid, beta-carotene, vitamin B6, zinc, nicotinamide or niacin, vitamin E and selenium and formulations thereof (Claims 6 - 9)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 98/01260

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0347056 A	20-12-1989	AU 618814 B	09-01-1992
		AU 3597489 A	14-12-1989
		AU 633442 B	28-01-1993
		CA 1334004 A	17-01-1995
		EP 0454102 A	30-10-1991
		ES 2053990 T	01-08-1994
		IE 63303 B	05-04-1995
		JP 2032017 A	01-02-1990
		JP 2796838 B	10-09-1998
		NZ 239126 A	27-07-1997
		US 4977187 A	11-12-1990
		US 5120760 A	09-06-1992
WO 9634846 A	07-11-1996	AU 5507996 A	21-11-1996
		AU 5508096 A	21-11-1996
		AU 5508196 A	21-11-1996
		BG 102011 A	29-05-1998
		BG 102012 A	29-05-1998
		BR 9606604 A	16-09-1997
		CA 2218699 A	07-11-1996
		CA 2218702 A	07-11-1996
		CA 2220091 A	07-11-1996
		EP 0823895 A	18-02-1998
		EP 0823889 A	18-02-1998
		EP 0823897 A	18-02-1998
		WO 9634855 A	07-11-1996
		WO 9634858 A	07-11-1996
		NO 975035 A	22-12-1997
		NO 975036 A	17-12-1997
		PL 323152 A	16-03-1998
		PL 323176 A	16-03-1998
WO 9634855 A	07-11-1996	AU 5507996 A	21-11-1996
		AU 5508096 A	21-11-1996
		AU 5508196 A	21-11-1996
		BG 102011 A	29-05-1998
		BG 102012 A	29-05-1998
		BR 9606604 A	16-09-1997
		CA 2218699 A	07-11-1996
		CA 2218702 A	07-11-1996

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 98/01260

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9634855 A		CA 2220091 A	07-11-1996
		EP 0823895 A	18-02-1998
		EP 0823889 A	18-02-1998
		EP 0823897 A	18-02-1998
		WO 9634846 A	07-11-1996
		WO 9634858 A	07-11-1996
		NO 975035 A	22-12-1997
		NO 975036 A	17-12-1997
		PL 323152 A	16-03-1998
		PL 323176 A	16-03-1998
EP 0440341 A	07-08-1991	AU 638525 B	01-07-1993
		AU 6925691 A	25-07-1991
		CA 2033823 A	19-07-1991
		DE 69100724 D	20-01-1994
		DE 69100724 T	28-04-1994
		DK 440341 T	14-02-1994
		ES 2060290 T	16-11-1994
		HK 74994 A	05-08-1994
		IE 67622 B	17-04-1996
		JP 7033655 A	03-02-1995
		US 5116624 A	26-05-1992
FR 2749133 A	05-12-1997	NONE	